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> d his

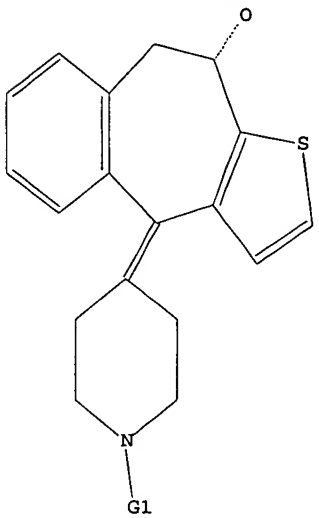
(FILE 'HOME' ENTERED AT 13:59:01 ON 19 MAR 2003)

FILE 'SCISEARCH' ENTERED AT 13:59:10 ON 19 MAR 2003
E BREYER-PFAFF/AU
E PFAFF
E PFAFF U/AU
L1 14 S E3
L2 0 S L1 AND KETOTIFEN
L3 2 S STEREOSELECTIVE AND KETOTIFEN

FILE 'REGISTRY' ENTERED AT 14:13:25 ON 19 MAR 2003
L4 STRUCTURE UPLOADED
L5 1 S L4
L6 86 S L4 SSS FULL

FILE 'CAPLUS' ENTERED AT 14:16:04 ON 19 MAR 2003
L7 754 S L6
L8 16 S L7 AND (STEREOISOMER? OR ENANTIOMER? OR RACEMIC OR RECEMATE O

=> d 14
L4 HAS NO ANSWERS
L4 STR



G1 H,Me

Structure attributes must be viewed using STN Express query preparation.

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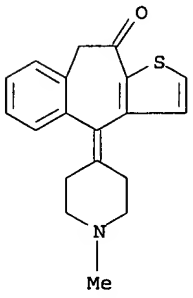
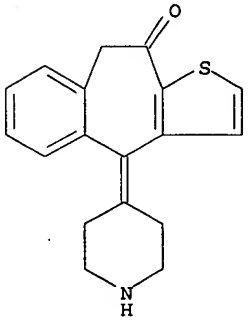
=> d 1-16 bib abs hitstr

L8 ANSWER 1 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 2002:205799 CAPLUS
DN 137:37774
TI Nonaqueous capillary electrophoretic separation of basic **enantiomers** using octakis(2,3-O-dimethyl-6-O-sulfo)-.gamma.-cyclodextrin, a new, single-isomer chiral resolving agent
AU Busby, M. Brent; Maldonado, Omar; Vigh, Gyula
CS Department of Chemistry, Texas A and M University, College Station, TX, 77842-3012, USA
SO Electrophoresis (2002), 23(3), 456-461
CODEN: ELCTDN; ISSN: 0173-0835
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
AB The **enantiomers** of 34 pharmaceutical weak-base analytes were sepd. by nonaq. capillary electrophoresis in acidic methanol background electrolytes using the sodium salt of the new, single-isomer chiral resolving agent, octakis(2,3-O-dimethyl-6-O-sulfo)-.gamma.-cyclodextrin (ODMS). The effective mobilities, sepn. selectivities and peak resoln. values of the weak-base analytes were detd. as a function of the ODMS concn. in the 0-40 mM range and were found to follow the theor. predictions of the charged resolving agent migration model (CHARM model) modified for ionic strength effects. Fast, efficient sepns. were achieved for both comparatively small and large **enantiomers**.
IT **34580-13-7**, Ketotifen **330679-71-5** **330679-72-6**
RL: ANT (Analyte); ANST (Analytical study)
(nonaq. capillary electrophoretic sepn. of basic **enantiomers** using octakis(2,3-O-di-Me-6-O-sulfo)-.gamma.-cyclodextrin as chiral resolving agent)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)

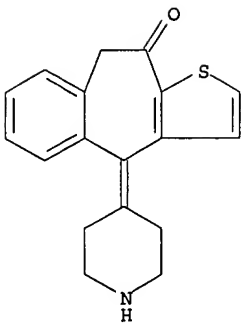


RN 330679-71-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)-, (4R)- (9CI) (CA INDEX NAME)



RN 330679-72-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)-, (4S)- (9CI) (CA INDEX NAME)

10069663



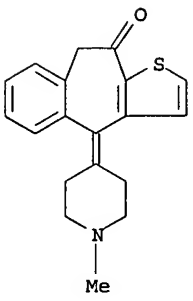
RE.CNT 18 THERE ARE 18 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 2 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 2001:208107 CAPLUS
DN 134:242680
TI Optically active isomers of ketotifen and therapeutically active metabolites thereof
IN Aberg, A. K. Gunnar; Wright, George E.; Chen, Jan L.; Maioli, Andrew T.
PA Bridge Pharma, Inc., USA
SO PCT Int. Appl., 27 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 2001019367	A1	20010322	WO 2000-US24892	20000912
	W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW, AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG				
	BR 2000013935	A	20020514	BR 2000-13935	20000912
	EP 1218007	A1	20020703	EP 2000-966709	20000912
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL				
	JP 2003509369	T2	20030311	JP 2001-523001	20000912
PRAI	US 1999-153566P	P	19990913		
	US 2000-197363P	P	20000415		
	US 2000-197905P	P	20000415		
	US 2000-197906P	P	20000415		
	US 2000-197985P	P	20000415		
	WO 2000-US24892	W	20000912		

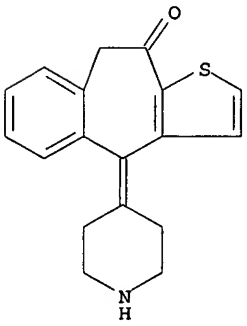
OS MARPAT 134:242680
AB **Racemic** norketotifen, 10-hydroxy-ketotifen, or 10-hydroxy-nor-ketotifen, and optically active isomers of ketotifen, norketotifen, 10-hydroxy-ketotifen and 10-hydroxy-norketotifen were found to have antiallergic and anti-inflammatory effects while being devoid of the severe dose-limiting sedative side effects of ketotifen. Prepn. of R and S isomers of norketotifen as well as their fumarates was presented.
IT **34580-13-7**, Ketotifen
RL: ADV (Adverse effect, including toxicity); BSU (Biological study, unclassified); BIOL (Biological study)
(antiallergic and anti-inflammatory effects of optically active isomers of ketotifen and therapeutically active metabolites)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)

This appl.

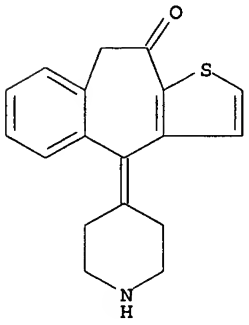


IT **330679-71-5P**, (R)-Norketotifen **330679-72-6P**, (S)-Norketotifen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); RACT (Reactant or reagent); USES (Uses)
(antiallergic and anti-inflammatory effects of optically active isomers of ketotifen and therapeutically active metabolites)

RN 330679-71-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)-, (4R)- (9CI) (CA INDEX NAME)

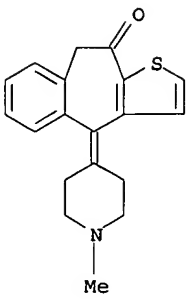


RN 330679-72-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)-, (4S)- (9CI) (CA INDEX NAME)



IT **116655-76-6**, (-)-Ketotifen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); RCT (Reactant); THU (Therapeutic use); BIOL (Biological study); RACT (Reactant or reagent); USES (Uses)
(antiallergic and anti-inflammatory effects of optically active isomers of ketotifen and therapeutically active metabolites)

RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)



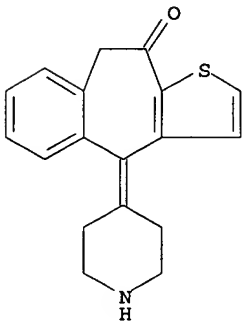
IT **330679-73-7P**, (R)-Norketotifen fumarate **330679-74-8P**, (S)-Norketotifen fumarate
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(antiallergic and anti-inflammatory effects of optically active isomers of ketotifen and therapeutically active metabolites)

RN 330679-73-7 CAPLUS

CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)-, (4R)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

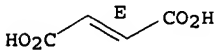
CRN 330679-71-5
CMF C18 H17 N O S



CM 2

CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

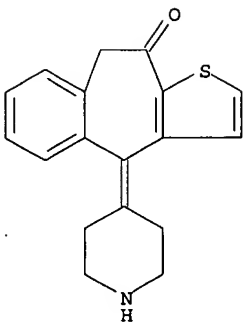


RN 330679-74-8 CAPLUS

CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)-, (4S)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

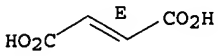
CRN 330679-72-6
CMF C18 H17 N O S



CM 2

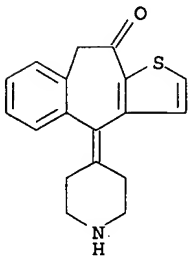
CRN 110-17-8
CMF C4 H4 O4

Double bond geometry as shown.

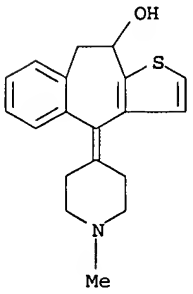


IT **34580-20-6**, Norketotifen **43076-12-6** **79987-41-0**
, 10-Hydroxynorketotifen **330679-75-9** **330679-76-0**
330679-77-1 **330679-78-2** **330679-79-3**
330679-80-6 **330679-81-7** **330679-82-8**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(antiallergic and anti-inflammatory effects of optically active isomers of ketotifen and therapeutically active metabolites)

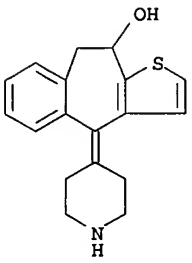
RN 34580-20-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)- (9CI) (CA INDEX NAME)



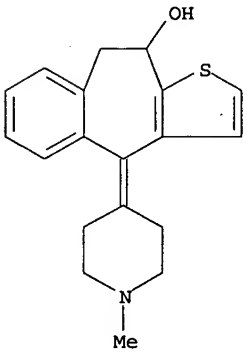
RN 43076-12-6 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



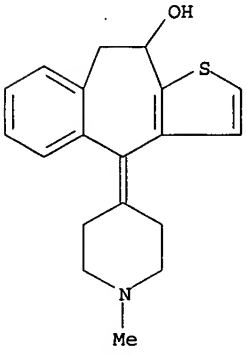
RN 79987-41-0 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(4-piperidinylidene)- (9CI) (CA INDEX NAME)



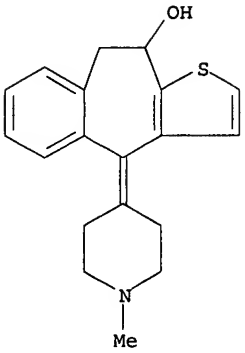
RN 330679-75-9 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)-, (4R,10R)- (9CI) (CA INDEX NAME)



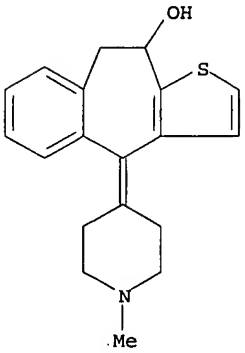
RN 330679-76-0 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)-, (4R,10S)- (9CI) (CA INDEX NAME)



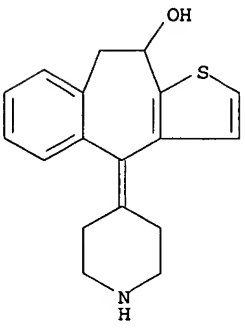
RN 330679-77-1 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)-, (4S,10R)- (9CI) (CA INDEX NAME)



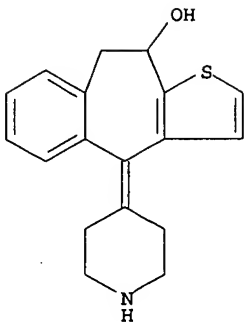
RN 330679-78-2 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)-, (4S,10S)- (9CI) (CA INDEX NAME)



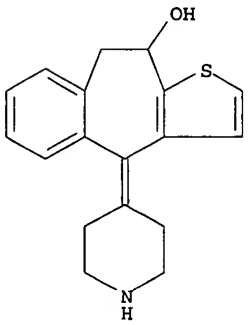
RN 330679-79-3 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(4-piperidinylidene)-, (4R,10R)- (9CI) (CA INDEX NAME)



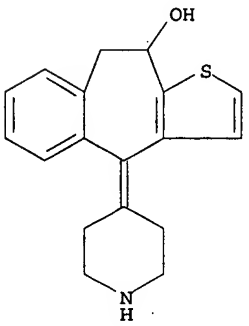
RN 330679-80-6 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(4-piperidinylidene)-, (4R,10S)- (9CI) (CA INDEX NAME)



RN 330679-81-7 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(4-piperidinylidene)-, (4S,10R)- (9CI) (CA INDEX NAME)

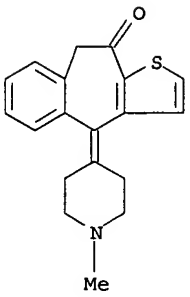


RN 330679-82-8 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(4-piperidinylidene)-, (4S,10S)- (9CI) (CA INDEX NAME)



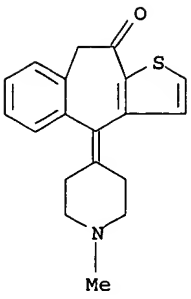
IT **116655-75-5**, (+)-Ketotifen
RL: RCT (Reactant); RACT (Reactant or reagent)
(antiallergic and anti-inflammatory effects of optically active isomers of ketotifen and therapeutically active metabolites)
RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)

10069663

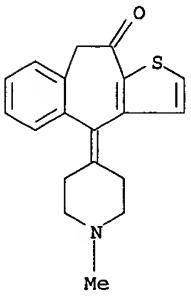


RE.CNT 4 THERE ARE 4 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

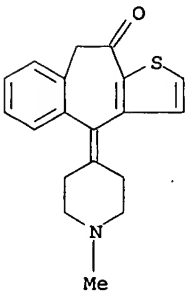
L8 ANSWER 3 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 2000:522238 CAPLUS
DN 133:202547
TI Comparative N-glucuronidation kinetics of ketotifen and amitriptyline by expressed human UDP-glucuronosyltransferases and liver microsomes
AU Breyer-Pfaff, Ursula
CS Department of Toxicology, University of Tuebingen, Tuebingen, D-72074, Germany
SO Drug Metabolism and Disposition (2000), 28(8), 869-872
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB Like other basic amphiphilic drugs, the (S)-enantiomer of the antiallergic drug ketotifen exhibited biphasic kinetics when it was converted to two isomeric quaternary ammonium-linked glucuronides in human liver microsomes. For (R)-ketotifen this applied when incubations were carried out in the absence of a detergent. Two UDP-glucuronosyltransferases (UGTs) present in human liver, UGT1A4 and UGT1A3, were previously shown to catalyze tertiary amine N-glucuronidation when expressed in HK293 cells. Therefore, the conjugation kinetics of (R)- and (S)-ketotifen were investigated with the two expressed proteins. When homogenates of HK293 cells expressing UGT1A4 were incubated without detergent, N-glucuronidation kinetics were monophasic with KM values of 59 .+-. 5 .mu.M for (R)- and 86 .+-. 26 .mu.M for (S)-ketotifen. In expts. with membranes contg. expressed UGT1A3, somewhat higher KM values were obtained. These values correspond to the high rather than to the low KM components of ketotifen glucuronidation in liver microsomes, the latter exhibiting KM values around 2 and 1 .mu.M, resp., with (R)- and (S)-ketotifen. With amitriptyline as the substrate, N-glucuronidation kinetics in the absence of detergent were biphasic in human liver microsomes and monophasic with a high KM value in cell homogenates contg. UGT1A4. The results suggest that UGT1A4 and UGT1A3 catalyze high-KM N-glucuronidation of tertiary amine drugs, whereas the low-KM reaction requires either an alternative enzyme or a special conformation of UGT1A4 or UGT1A3 that can be attained in liver microsomes, but not in HK293 cell membranes.
IT **34580-13-7**, Ketotifen **116655-75-5**, 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, R- **116655-76-6**, 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, S-
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(comparative N-glucuronidation kinetics of ketotifen and amitriptyline by expressed human UDP-glucuronosyltransferases and liver microsomes)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)



RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)



RE.CNT 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 4 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1999:793640 CAPLUS
DN 132:146125
TI High-affinity **stereoselective** reduction of the **enantiomers** of ketotifen and of ketonic nortriptyline metabolites by aldo-keto reductases from human liver
AU Breyer-Pfaff, U.; Nill, K.
CS Department of Toxicology, University of Tuebingen, Tuebingen, D-72074, Germany
SO Biochemical Pharmacology (1999), Volume Date 2000, 59(3), 249-260
CODEN: BCPCA6; ISSN: 0006-2952
PB Elsevier Science Inc.
DT Journal
LA English
AB Aldo-keto reductases (AKR) form an enzyme superfamily catalyzing the redn. of carbonyl compds. and in some cases the reverse oxidn. of alcs. as well. In particular, a role in drug metab. has been considered for the AKR1C family, but published data failed to reveal low Km drug substrates. Moreover, structure-activity relationships using chem. related substrates have not been established. In the present investigation, a modified

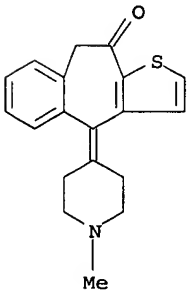
1449

not prior art

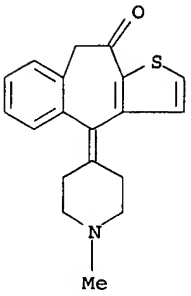
procedure was developed for the isolation of AKR1C1, 1C2, and 1C4 (dihydrodiol dehydrogenases 1, 2, and 4) from human liver cytosol along with carbonyl reductase (EC 1.1.1.184), a member of the short-chain alc. dehydrogenase superfamily. The kinetics of NADPH-dependent redn. by the closely related enzymes AKR1C1 and 1C2 were studied with the structurally similar substrates (R)- and (S)-ketotifen and E- and Z-10-oxonortriptyline by HPLC measurement of the products. Km values varied between 2.6 and 53 .mu.M and Vmax values between 5 and 313 mU/mg protein; substrate inhibition with Ki around 30 .mu.M occurred in the redn. of E- and Z-10-oxonortriptyline by AKR1C1. The reactions were strictly stereospecific with prodn. of one **enantiomeric** alc. from each ketotifen **enantiomer** and of the (+)-**enantiomers** of E- and Z-10-hydroxynortriptyline. Enzymic NADP+-dependent oxidn. of the alcs. mirrored the redn. with regard to stereochem. specificity. All four ketones were no or poor substrates of carbonyl reductase, whereas haloperidol was reduced by this enzyme with low affinity, but high efficiency.

IT **116655-75-5 116655-76-6 258270-54-1**
258270-55-2
RL: BPR (Biological process); BSU (Biological study, unclassified); MFM (Metabolic formation); BIOL (Biological study); FORM (Formation, nonpreparative); PROC (Process)
(high-affinity **stereoselective** redn. of **enantiomers** of ketotifen and of ketonic nortriptyline metabolites by aldo-keto reductases from human liver)

RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)



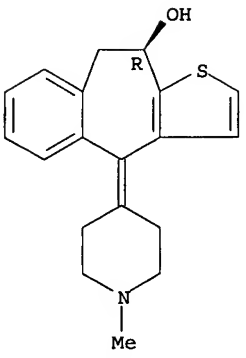
RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)



RN 258270-54-1 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)-, (10R)- (9CI) (CA INDEX NAME)

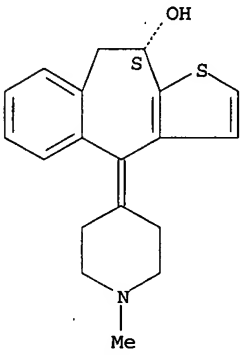
Absolute stereochemistry.

10069663



RN 258270-55-2 CAPLUS
CN 4H-Benzo[4,5]cyclohepta[1,2-b]thiophene-10-ol, 9,10-dihydro-4-(1-methyl-4-piperidinylidene)-, (10S)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.



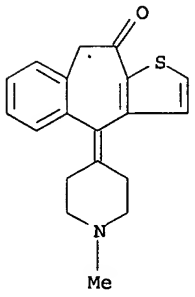
RE.CNT 41 THERE ARE 41 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 5 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1999:710251 CAPLUS
DN 132:44451
TI Conjugation of the **enantiomers** of ketotifen to four isomeric quaternary ammonium glucuronides in humans in vivo and in liver microsomes
AU Mey, Udo; Wachsmuth, Helmut; Breyer-Pfaff, Ursula
CS Department of Toxicology, University of Tuebingen, Tuebingen, D-72074, Germany
SO Drug Metabolism and Disposition (1999), 27(11), 1281-1292
CODEN: DMDSAI; ISSN: 0090-9556
PB American Society for Pharmacology and Experimental Therapeutics
DT Journal
LA English
AB The antiallergic drug ketotifen is chiral due to a nonplanar seven-membered ring contg. a keto group. Earlier studies have revealed glucuronidation at the tertiary amino group as a major metabolic pathway in humans. Chem. synthesis of glucuronides from **racemic** ketotifen now led to four isomers separable by HPLC of which two each could be ascribed to (R)-(+)- and (S)-(-)-ketotifen by synthesis from the **enantiomers**. According to 1H NMR anal. of the (S)-ketotifen N-glucuronides, the conformation of the piperidylidene ring differs between the two isomers. Enzymic hydrolysis with Escherichia coli .beta.-glucuronidase proceeded at a lower rate with the slower eluting (S)-ketotifen glucuronide than with the three other isomers. On incubation of the ketotifen **enantiomers** (0.5-200 .mu.M) with human liver microsomes in the presence of UDP-glucuronic acid and Triton X-100, the N-glucuronides of (R)-ketotifen were produced with an apparent KM 15 .mu.M and Vmax 470 pmol/min/mg protein. The two (S)-ketotifen glucuronides were formed by two-enzyme kinetics with KM1 1.3 .mu.M and KM2 92 .mu.M and Vmax values of 60 and 440 pmol/min/mg protein. After ingestion of 1 mg of **racemic** ketotifen, 10 healthy subjects excreted in urine 17 .+-. 5% of the dose in the form of N-glucuronides. The (R)-ketotifen glucuronide isomers contributed one-sixth only, whereas the remainder consisted primarily of the (S)-ketotifen glucuronide isomer, which eluted last. Differential hydrolysis or membrane transport may be

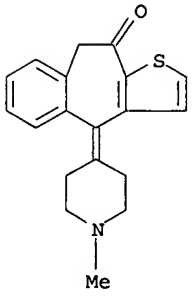
responsible for the discrepancy between N-glucuronide isomer ratios in vitro and in vivo.

IT **34580-13-7**, Ketotifen **116655-75-5**, (R)-Ketotifen **116655-76-6**
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(conjugation of the **enantiomers** of ketotifen to four isomeric quaternary ammonium glucuronides in humans in vivo and in liver microsomes)

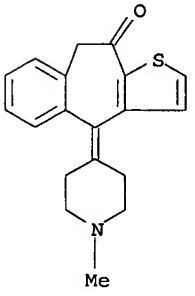
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)



RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)

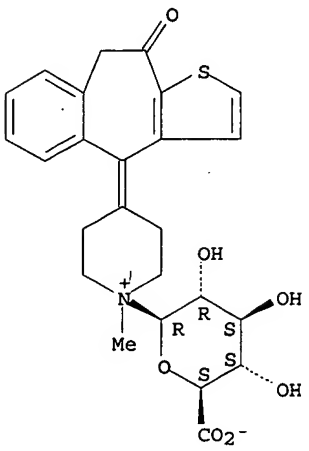


IT **81759-45-7P 252719-79-2P 252719-80-5P**
RL: BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(conjugation of the **enantiomers** of ketotifen to four isomeric quaternary ammonium glucuronides in humans in vivo and in liver microsomes)

RN 81759-45-7 CAPLUS
CN Piperidinium, 4-(9,10-dihydro-10-oxo-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-.beta.-D-glucopyranuronosyl-1-methyl-, inner salt

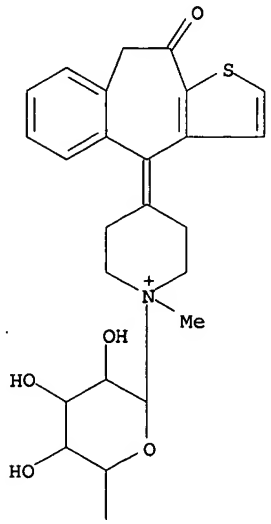
(9CI) (CA INDEX NAME)

Absolute stereochemistry.



RN 252719-79-2 CAPLUS
CN Piperidinium, 4-(9,10-dihydro-10-oxo-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-.beta.-D-glucopyranuronosyl-1-methyl-, inner salt, stereoisomer (9CI) (CA INDEX NAME)

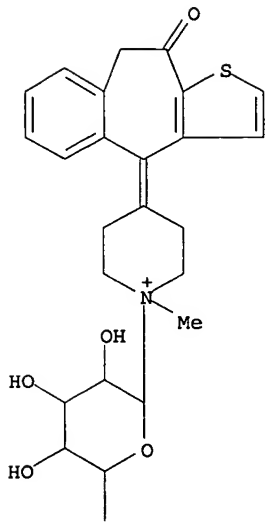
PAGE 1-A



PAGE 2-A

RN 252719-80-5 CAPLUS
CN Piperidinium, 4-(9,10-dihydro-10-oxo-4H-benzo[4,5]cyclohepta[1,2-b]thiophen-4-ylidene)-1-.beta.-D-glucopyranuronosyl-1-methyl-, inner salt, stereoisomer (9CI) (CA INDEX NAME)

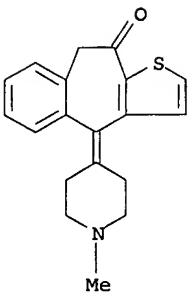
PAGE 1-A



PAGE 2-A

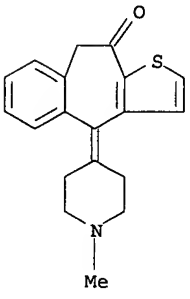
RE.CNT 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 6 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1999:675016 CAPLUS
DN 132:26950
TI Nonaqueous capillary electrophoretic separation of basic **enantiomers** using heptakis(2,3-dimethyl-6-sulfato)-.beta.-cyclodextrin
AU Tacker, Matthew; Glukhovskiy, Pavel; Cai, Hong; Vigh, Gyula
CS Department of Chemistry, Texas A and M University, College Station, TX, 77842-3012, USA
SO Electrophoresis (1999), 20(13), 2794-2798
CODEN: ELCTDN; ISSN: 0173-0835
PB Wiley-VCH Verlag GmbH
DT Journal
LA English
AB The **enantiomers** of 40 basic analytes, mostly pharmaceuticals, were sepd. by nonaq. capillary electrophoresis in acidic methanol background electrolytes using the sodium salt of heptakis(2,3-dimethyl-6-sulfato)-.beta.-cyclodextrin (HDMS-.beta.-CD). The effective mobilities, sepn. selectivities, and peak resoln. values were detd. as a function of the HDMS-.beta.-CD concn. in the 0-40 mM range and were found to follow the theor. predictions of the charged resolving agent migration model (CHARM model). Fast, efficient **enantiomer** sepns. were achieved for a large no. of both very hydrophobic and hydrophilic weak bases.
IT **34580-13-7**
RL: ANT (Analyte); ANST (Analytical study)
(sepn. of basic drugs by nonaq. capillary electrophoresis using heptakis(2,3-dimethyl-6-sulfato)-.beta.-cyclodextrin as chiral selector)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



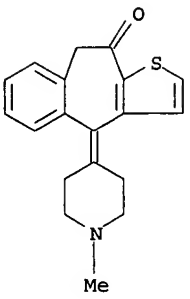
RE.CNT 30 THERE ARE 30 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 7 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1999:609250 CAPLUS
DN 132:131712
TI **Stereoselective** high-affinity reduction of ketonic nortriptyline metabolites and of ketotifen by aldo-keto reductases from human liver
AU Breyer-Pfaff, Ursula; Nill, Karl
CS Department of Toxicology, University of Tuebingen, Tuebingen, D-72074, Germany
SO Advances in Experimental Medicine and Biology (1999), 463(Enzymology and Molecular Biology of Carbonyl Metabolism 7), 473-480
CODEN: AEMBAP; ISSN: 0065-2598
PB Kluwer Academic/Plenum Publishers
DT Journal
LA English
AB Aldo-keto reductases (AKR1C1 and 1C2) and carbonyl reductase were isolated from human liver and the redn. of substrates, ketonic nortriptyline metabolites and ketotifen, was studied. The structurally similar substrates Z- and E-10-oxo-nortriptyline and (+)- and (-)-ketotifen were distinguished by their low Km values of 2.6-53 .mu.M. The stereoselectivity of the high-affinity redn. of these substrates may make them appropriate tools for the elucidation of the active site structure of the enzymes. AKR1C1 apparently possesses an addnl. binding site with relatively high affinity the occupation of which results in an inhibition of the catalytic activity.
IT **116655-75-5**, (+)-Ketotifen **116655-76-6**, (-)-Ketotifen
RL: BPR (Biological process); BSU (Biological study, unclassified); BIOL (Biological study); PROC (Process)
(**stereoselective** high-affinity redn. of ketonic nortriptyline metabolites and ketotifen by aldo-keto reductases from human liver)
RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)



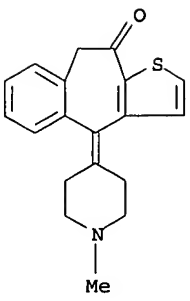
RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)

10069663



RE.CNT 17 THERE ARE 17 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 8 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1999:297968 CAPLUS
DN 131:223210
TI Mast cell degranulation in rat mesenteric venule: effects of l -name, methylene blue and ketotifen
AU Kimura, Masakki; Mitani, Hironobu; Bandoh, Tsutomu; Totsuka, Tetsuya; Hayashi, Shigehiro
CS Department of Pharmacology, Sandoz Tsukuba Research Institute, Tsukuba, 300-2611, Japan
SO Pharmacological Research (1999), 39(5), 397-402
CODEN: PHMREP; ISSN: 1043-6618
PB Academic Press
DT Journal
LA English
AB Mast cells are present in proximity to the microvessels, and on stimulation with inhibition of NO synthesis, are a rich source of numerous inflammatory mediators. A microcirculatory study was undertaken to clarify whether nitric oxide (NO) and activation of guanylate cyclase is involved in degranulation of perivascular mast cells in the rat mesenteric venule, and whether oral administration of ketotifen suppress the degranulation. Intravital microscopy was used to monitor the rates of adherence and extravasation of leukocytes in single unbranched venules with diams. between 25 and 35 .mu.m of rat mesentery. Leukocyte rolling velocity, red blood cell velocity, vessel diam. and blood pressure were also measured. Mast cell degranulation was quantified within 30 .mu.m from the venule. L-NAME, at an i.v. dose of 30 mg kg-1, increased the no. of degranulated cells, while its **enantiomer**, D-NAME at the same dose had no effect. Superfusion with methylene blue (MB), an inhibitor of sol. guanylate cyclase, at 50 .mu.m elicited similar degranulation of the mast cells. The degranulation was assocd. with increased adhesion of leukocytes to the endothelium and the slowed rolling. Pretreatment with ketotifen at an oral dose of 1 mg kg-1 inhibited mast cell degranulation in responses to either L-NAME or MB. It is conceivable that guanylate cyclase for NO prodn. pathway in endothelial and/or mast cells is involved in the mast cell degranulation process, and the process or subsequent action of NO may be preserved by ketotifen, eliciting down-modulation of mast cell activation. (c) 1999 The Italian Pharmacological Society.
IT **34580-13-7**, Ketotifen
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(NO and guanylate cyclase involvement in mastocyte degranulation in mesenteric venule: ketotifen effect)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



RE.CNT 20 THERE ARE 20 CITED REFERENCES AVAILABLE FOR THIS RECORD
ALL CITATIONS AVAILABLE IN THE RE FORMAT

L8 ANSWER 9 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1995:401335 CAPLUS
DN 122:170225
TI Pharmaceutical compositions containing H2 antagonists and antihistamines
IN Sims, Robert T.; Slivka, William
PA Merck and Co., Inc., USA; McNeil-PPC, Inc.
SO PCT Int. Appl., 25 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9501792	A1	19950119	WO 1994-US7528	19940705
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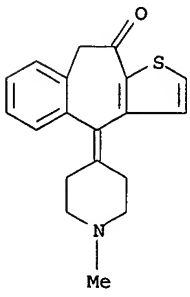
	RW: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
	AU 9472550	A1	19950206	AU 1994-72550	19940705
PRAI	US 1993-87940		19930706		
	WO 1994-US7528		19940705		

AB Pharmaceutical compns. for use in the prevention, treatment and relief of mild to moderate stomach and esophagus disorders such as indigestion, sour stomach, and heartburn while also treating symptoms assocd. with colds, flu and allergies comprise (1) an amt. effective in the relief of gastrointestinal or esophagus disorders of an H2 antagonist selected from famotidine (I) and pharmaceutically acceptable salts, hydrates, **stereoisomers** or polymorphs thereof, and (2) .gtoreq.1 antihistamine or a therapeutically active **stereoisomer** thereof or a pharmaceutically acceptable salt, hydrate, or polymorph thereof, and optionally (3) an antiflatulent amt. of a compd. selected from simethicone, alpha-D-galactosidase, and a silicon based antiflatulent; with the proviso that NSAIDs or proton-pump inhibitors are not included. A tablet contained I 40, diphenidramine.HCl 50, PVP 15, Avicel PH101 40, Ma stearate 4mg.

IT **34580-13-7**, Ketotifen
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. contg. H2 antagonists and antihistamines)

RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



10069663

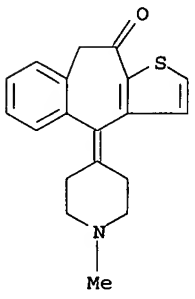
L8 ANSWER 10 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1993:16318 CAPLUS
DN 118:16318
TI Beta2-sympathomimetic **enantiomers** as side effect-free bronchodilators
IN Morley, John
PA Sandoz-Patent-G.m.b.H., Germany
SO Ger. Offen., 10 pp.
CODEN: GWXXBX
DT Patent
LA German
FAN.CNT 2

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	DE 4209989	A1	19921008	DE 1992-4209989	19920327
	CH 685672	A	19950915	CH 1992-1045	19920401
	CH 686869	A	19960731	CH 1995-2592	19920401
	FR 2674751	A1	19921009	FR 1992-4148	19920402
	FR 2674751	B1	19950505		
	BE 1005778	A5	19940125	BE 1992-309	19920402
	CA 2065051	AA	19921006	CA 1992-2065051	19920403
	NL 9200629	A	19921102	NL 1992-629	19920403
	GB 2255503	A1	19921111	GB 1992-7363	19920403
	GB 2255503	B2	19951206		
	JP 05097707	A2	19930420	JP 1992-81971	19920403
	GB 2289842	A1	19951206	GB 1995-17463	19920403
	GB 2289842	B2	19960131		
	US 2002132830	A1	20020919	US 2002-95846	20020312
PRAI	GB 1991-7196	A	19910405		
	GB 1992-7363	A3	19920403		
	US 1992-862907	B1	19920403		
	US 1994-223798	B1	19940406		
	US 1995-382744	B3	19950202		
	US 1997-972526	B1	19971118		
	US 2000-550039	B1	20000414		

AB Inflammatory and obstructive respiratory diseases are treated with **enantiomeric** .beta.2-sympathomimetic bronchodilators. Use of the **enantiomers** avoids the side effects assocd. with the administration of the corresponding **racemic** drugs. Patients with asthma, administered 20 .mu.g (R, S)-albuterol by inhalation 2-4 times per day for 1-6 mo, showed hyperactivity of the respiratory tract. No such effect was obsd., however, when 100 .mu.g (R)-albuterol was administered instead of the **racemic** compd.

IT **34580-13-7**, Ketotifen
RL: BIOL (Biological study)
(bronchodilators contg. **enantiomers** of .beta.2-sympathomimetic drugs and, side effect-free)

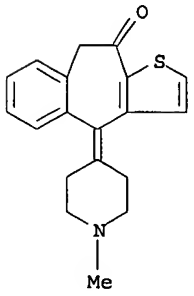
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



L8 ANSWER 11 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1992:400623 CAPLUS
DN 117:623
TI Effects of BRL 38227 on neurally-mediated responses in the guinea pig isolated bronchus
AU Good, D. M.; Clapham, J. C.; Hamilton, T. C.
CS SmithKline Beecham Pharm., Pinnacles/Harlow/Essex, CM19 5AD, UK
SO British Journal of Pharmacology (1992), 105(4), 933-40
CODEN: BJPCBM; ISSN: 0007-1188
DT Journal

10069663

LA English
AB In guinea-pig isolated bronchus treated with indomethacin (2.8 .mu.M), elec. field stimulation (EFS; 10 Hz, 0.5 ms, 60-70 V, for 10 s) evoked a tetrodotoxin (3 .mu.M)-sensitive, biphasic contraction comprising a rapid, atropine (1 .mu.M)-sensitive cholinergic response succeeded by a slowly developing, capsaicin (10 .mu.M)-sensitive, nonadrenergic, noncholinergic excitatory (NANCe) response. BRL 38227 (0.3-3 .mu.M), salmeterol (0.003-3 .mu.M) and ketotifen (1.0-300 .mu.M) each produced concn.-dependent inhibition of both NANCe and cholinergic responses to EFS in guinea-pig isolated bronchus. Substance P (SP; 1 .mu.M) and neurokinin A (NKA; 0.07 .mu.M) produced contractions equiv. in magnitude to the NANCe response to EFS, which were inhibited by salmeterol (1 .mu.M), but not by BRL 38227 (3 .mu.M) or ketotifen (100 .mu.M). Acetylcholine (ACh; 6 .mu.M) was equi-effective with the elec. activation of cholinergic neurons. BRL 38227 (3 .mu.M) slightly inhibited responses to ACh (6 .mu.M). Salmeterol (1 .mu.M) and ketotifen (100 .mu.M) markedly inhibited responses to ACh (6 .mu.M). In bronchial rings pre-contracted with ACh (100 .mu.M), BRL 38227 (0.1-30 .mu.M), salmeterol (0.001-3 .mu.M) and ketotifen (0.1-100 .mu.M) each produced concn.-dependent relaxation. Unlike ketotifen, BRL 38227 and salmeterol only partially (18.8% and 51.8% resp.) reversed the ACh-induced contraction. The (+)-analog of BRL 38227, BRL 38226 (0.3-100 .mu.M), was without effect on responses to EFS and had no effect on the inhibition caused by BRL 38227. The K+-channel activators pinacidil (3.0-30 .mu.M) and RP 52891 (3.0-30 .mu.M) exerted similar inhibitory actions on responses to EFS as BRL 38227, but were less potent. Glibenclamide (0.1-1.0 .mu.M) and phentolamine (3 .mu.M) antagonized the inhibitory effects of BRL 38227 on responses to EFS. It is concluded that BRL 38227 and ketotifen can inhibit NANCe neuroeffector transmission at concns. exerting little or no inhibitory effects on responses to exogenously applied tachykinins. By contrast, in addn. to suppressing NANCe responses to EFS, salmeterol also markedly inhibits responses to SP and NKA. At concns. markedly suppressing cholinergic neuroeffector transmission, BRL 38227 has only minor effects on responses to exogenously-applied ACh. Salmeterol and ketotifen both depress responses to ACh within the concn.-range over which they inhibit cholinergic responses to EFS. The inhibitory effects of BRL 38227 on responses to EFS exhibit stereo-specificity and may involve the opening of a neuronal K+-channel. This K+-channel is glibenclamide- and phentolamine-sensitive and appears similar to the smooth muscle K+-channel which is modulated by BRL 38227.
IT **34580-13-7**, Ketotifen
RL: BIOL (Biological study)
(antiasthmatic activity of, inhibition of neurally-mediated bronchoconstriction in)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



L8 ANSWER 12 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1991:694112 CAPLUS
DN 115:294112
TI Selected applications of cyclodextrin selectors in capillary electrophoresis
AU Snopek, Jiri; Soini, Helena; Novotny, Milos; Smolkova-Keulemansova, Eva; Jelinek, Ivan
CS Dep. Chem., Indiana Univ., Bloomington, IN, 47405, USA
SO Journal of Chromatography (1991), 559(1-2), 215-22
CODEN: JOCRAM; ISSN: 0021-9673
DT Journal
LA English
AB Through the use of .alpha.-, .beta.-, .gamma.- and heptakis(2,6-di-O-

methyl)-.beta.-cyclodextrin as stereospecific selectors or electrolyte modifiers, both in capillary zone electrophoresis and isotachophoresis, selected model isomeric compds. (including optical isomers of pharmaceutical interest) were resolved. Sol. alkylhydroxyalkylcellulose derivs. were further added to the cyclodextrin-modified background electrolytes under study. Their presence was found to be essential, as demonstrated by improvements in both enantioselectivity and sepn. efficiency. The results obtained in both electrophoretic modes, under optimized conditions, are compared and discussed.

IT **137754-48-4**
RL: ANST (Analytical study); PROC (Process)
(resoln. of, by cyclodextrin-assisted capillary zone electrophoresis)

RN 137754-48-4 CAPLUS

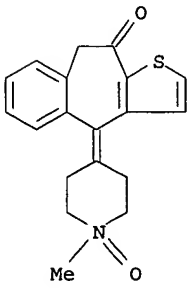
IT **116655-74-4**
RL: ANST (Analytical study); PROC (Process)
(resoln. of, by cyclodextrin-assisted capillary zone electrophoresis and isotachophoresis)

RN 116655-74-4 CAPLUS

IT **137731-91-0 137731-92-1**
RL: ANST (Analytical study); PROC (Process)
(sepn. of, from **enantiomer** by cyclodextrin-assisted capillary zone electrophoresis)

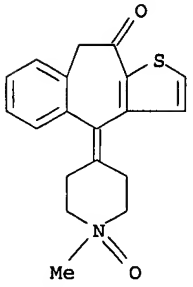
RN 137731-91-0 CAPLUS

CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-1-oxido-4-piperidinylidene)-, (+)- (9CI) (CA INDEX NAME)



RN 137731-92-1 CAPLUS

CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-1-oxido-4-piperidinylidene)-, (-)- (9CI) (CA INDEX NAME)

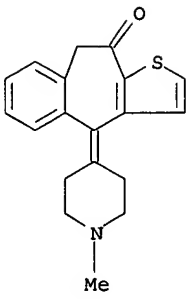


IT **116655-75-5 116655-76-6**
RL: ANST (Analytical study); PROC (Process)
(sepn. of, from **enantiomer** by cyclodextrin-assisted capillary zone electrophoresis and isotachophoresis)

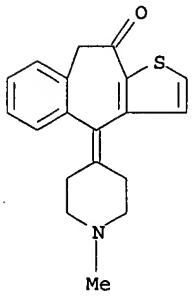
RN 116655-75-5 CAPLUS

CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)

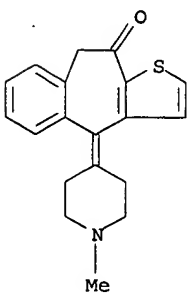
10069663



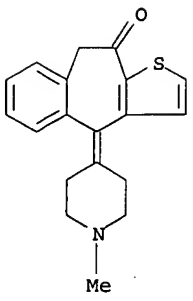
RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)



L8 ANSWER 13 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1991:687331 CAPLUS
DN 115:287331
TI Analytical study of ketotifen and some of its synthesis intermediates using cyclodextrin selectors in HPLC and isotachophoresis (ITP)
AU Bazant, L.; Snopek, J.; Jelinek, I.; Smolkova-Keulemansova, E.
CS Inst. Clin. Exp. Med., Prague, 146 22, Czech.
SO Minutes Int. Symp. Cyclodextrins, 5th (1990), 634-7. Editor(s): Duchene, Dominique. Publisher: Ed. Sante, Paris, Fr.
CODEN: 57LSAJ
DT Conference
LA English
AB Ketotifen **enantiomers** and some of their synthesis intermediates were sepd. using .beta.-cyclodextrin (.beta.-CD)-bonded HPLC stationary phase and .beta.-CD and heptakis(2,6-di-O-methyl-.beta.-CD (diMe-.beta.-CD) as modifiers in the leading electrolyte in capillary isotachophoresis (ITP). Sepn. conditions were optimized and analyses developed were applied to the control of optically enriched mixts., of the stability of pure **enantiomers** and of the ketotifen synthesis intermediates.
IT **34580-13-7**, Ketotifen
RL: ANST (Analytical study)
(detn. of synthetic intermediates and, cyclodextrin selectors in HPLC and isotachophoresis in)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



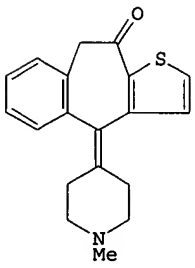
10069663



L8 ANSWER 14 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1990:440470 CAPLUS
DN 113:40470
TI Process for preparing pure **enantiomers** of 4-(1-methyl-4-piperidylidene)-4,9-dihydrobenzo[4,5]cyclohepta[1,2-b]thiophen-10-one as antihistaminics and antianaphylactics
IN Polivka, Zdenek; Protiva, Miroslav; Jelinek, Ivan; Snopek, Jiri; Smolkova-Keulemansova, Eva; Metys, Jan; Valchar, Martin
PA Czech.
SO Czech., 4 pp.
CODEN: CZXXA9
DT Patent
LA Czech
FAN.CNT 1

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
CS 263993	B1	19890512	CS 1988-1614	19880311

PRAI CS 1988-1614 19880311
OS MARPAT 113:40470
GI



I

AB Pure (+)- and (-)-I, antihistaminics and antianaphylactics having antimuscarinic activity, were sepd. from the **racemic** base (.+-.)-I (ketotifen) (II) by neutralization of II with optically active acids 4-RC6H5CO2CH(CO2H)CH(CO2H)O2CC6H4R-4 (III; R = H, Me) followed by repeated crystn. of the resulting diastereoisomeric salt mixt. from aq. EtOH to const. optical rotation. The salts were decompd. with NH4OH and the title **enantiomers** sepd. by extn. with solvents and evapn. Thus, 10.2 g (-)-O,O'-dibenzoyl-L-tartaric acid was added to 7,6 g II in 15 mL EtOH and the mixt. was left to crystallize for 20 days to give a diastereoisomeric salt mixt. m. 155.degree. which after three crystns. from 140, 120, and 100 mL 75% aq. EtOH resp. gave 8.5 g of a homogeneous diastereoisomeric salt m. 158-160.degree. from which 3.5 g of the free (+)-I m. 159-162.degree. was liberated. In a similar expt. from 12.9 g II, 7.2 g (-)-I was isolated via diastereoisomeric salt mixt. with (+)-III (R = H). In guinea pigs (+)-I and (-)-I inhibited histamine-induced bronchospasm with PD50 of 0.026 mg/kg and 0.013 mg/kg resp., orally. In rats (+)-I gave protection against anaphylactoid skin reaction induced by histamine-releasing substance 48/80 with PD50 of 4.2 mg/kg orally. In rat brain tissue in vitro, (+)-I, (-)-I, and II inhibited 0.5 nM (3H)quinuclidinylbenzylate with IC50 of 149, 1217, and 260 nM, resp.

IT **128044-20-2P 128111-48-8P 128111-49-9P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. and base liberation from, in resoln. of antihistaminic and antianaphylactic **enantiomer**)

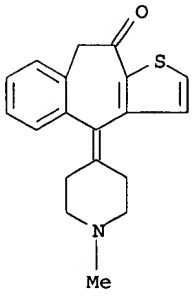
RN 128044-20-2 CAPLUS

10069663

CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, [R-(R*,R*)]-, compd. with 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cycloheptа[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

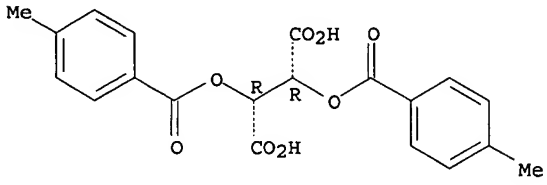
CRN 34580-13-7
CMF C19 H19 N O S



CM 2

CRN 32634-66-5
CMF C20 H18 O8

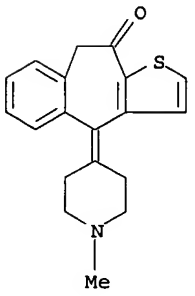
Absolute stereochemistry.



RN 128111-48-8 CAPLUS
CN Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with (+)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cycloheptа[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

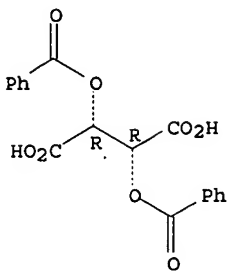
CRN 116655-75-5
CMF C19 H19 N O S



CM 2

CRN 2743-38-6
CMF C18 H14 O8

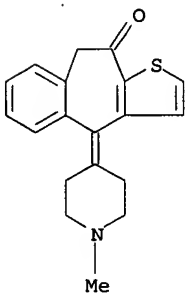
Absolute stereochemistry.



RN 128111-49-9 CAPLUS
CN Butanedioic acid, 2,3-bis(benzoyloxy)-, [S-(R*,R*)]-, compd. with (-)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

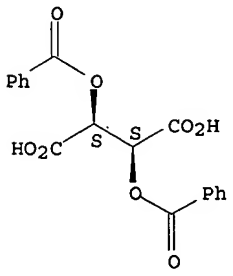
CRN 116655-76-6
CMF C19 H19 N O S



CM 2

CRN 17026-42-5
CMF C18 H14 O8

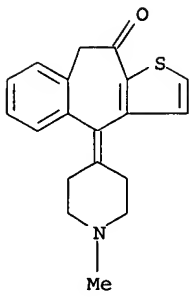
Absolute stereochemistry. Rotation (+).



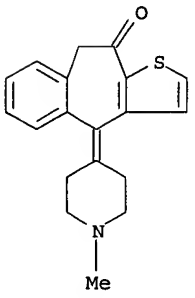
IT **116655-75-5P 116655-76-6P**
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of, as antihistaminic and antianaphylactic **enantiomers**)

RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)

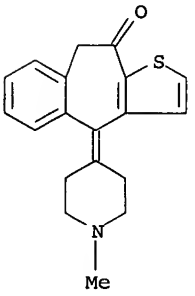
10069663



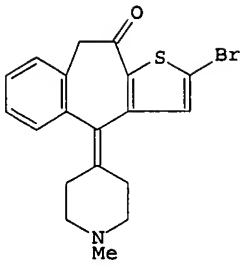
RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)



IT **34580-13-7**, Ketotifen
RL: PROC (Process)
(salt formation of, with optically active tartrate esters, in resoln. of antihistaminic and antianaphylactic **enantiomers**)
RN 34580-13-7 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



L8 ANSWER 15 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1990:216595 CAPLUS
DN 112:216595
TI 4H-Benzo[4,5-cyclohepta[1,2-b]thiophenes and 9,10-dihydro derivatives. Sulfonium analogs of pizotifen and ketotifen. Chirality of ketotifen. Synthesis of the 2-bromo derivative of ketotifen
AU Polivka, Zdenek; Budesinsky, Milos; Holubek, Jiri; Schneider, Bohdan; Sedivy, Zdenek; Svatek, Emil; Matousova, Oluse; Metys, Jan; Valchar, Martin; et al.
CS Res. Inst. Pharm. Biochem., Prague, 130 60, Czech.
SO Collection of Czechoslovak Chemical Communications (1989), 54(9), 2443-69
CODEN: CCCCAK; ISSN: 0010-0765
DT Journal
LA English
OS CASREACT 112:216595
GI

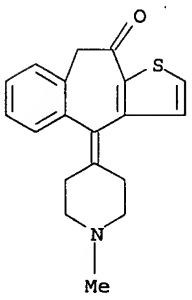


I

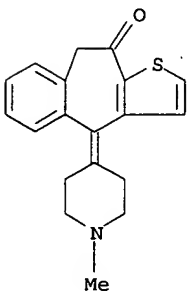
AB Sulfonium analogs of pizotifen and ketotifen were prepd. The chirality of ketotifen was proven by 1H NMR spectroscopy with the help of the optically active NMR shift reagent. The resoln. of **racemic** ketotifen (I) was achieved by crystn. of salts with optically active O,O'-diacyltartaric acids and homogeneous **enantiomers** were obtained. The X-ray crystallog. anal. of (+)-I (-)-O,O'-di(p-toluoyl)-(R)-tartrate led to the three-dimensional structure of the mol. of (+)-ketotifen which enabled to det. its abs. configuration to be (R). (R)(+)-ketotifen was found to be the more active ketotifen **enantiomer** but the stereoselectivity of its action is only a partial one. The 2-bromo deriv. of ketotifen, I, was prepd. and found to be much less active than ketotifen in the line of antihistamine activity.

IT **116655-75-5P 116655-76-6P 126939-29-5P**
RL: BAC (Biological activity or effector, except adverse); BSU (Biological study, unclassified); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(prepn. and biol. activity of)

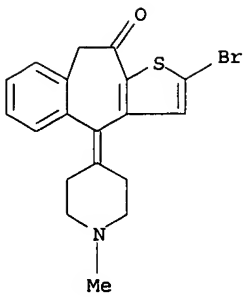
RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)



RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)



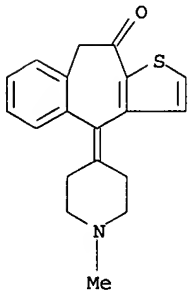
RN 126939-29-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 2-bromo-4,9-dihydro-4-(1-methyl-4-piperidinylidene)- (9CI) (CA INDEX NAME)



IT **127061-00-1P**
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and crystal structure of)
RN 127061-00-1 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, [R-(R*,R*)]-, compd. with (+)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

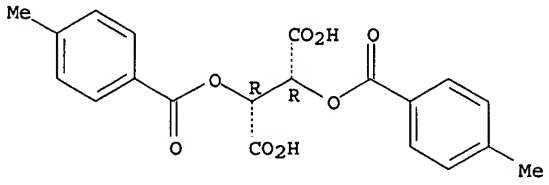
CRN 116655-75-5
CMF C19 H19 N O S



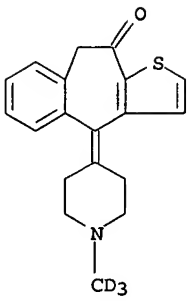
CM 2

CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry.



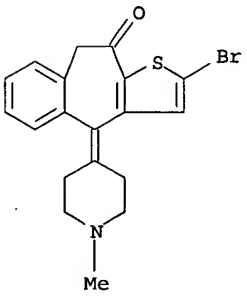
IT **126939-14-8P 126939-17-1P 126939-31-9P**
127060-95-1P 127060-96-2P 127060-97-3P
127060-98-4P 127060-99-5P 127061-01-2P
127061-02-3P
RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn. of)
RN 126939-14-8 CAPLUS
RN 126939-17-1 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-[1-(methyl-d3)-4-piperidinylidene]- (9CI) (CA INDEX NAME)



RN 126939-31-9 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 2-bromo-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (2E)-2-butenedioate (1:1) (9CI) (CA INDEX NAME)

CM 1

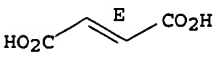
CRN 126939-29-5
CMF C19 H18 Br N O S



CM 2

CRN 110-17-8
CMF C4 H4 O4

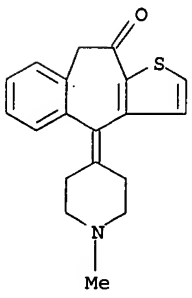
Double bond geometry as shown.



RN 127060-95-1 CAPLUS
CN Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1S)-, compd. with (-)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

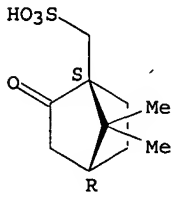
CRN 116655-76-6
CMF C19 H19 N O S



CM 2

CRN 3144-16-9
CMF C10 H16 O4 S

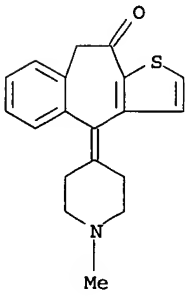
Absolute stereochemistry. Rotation (+).



RN 127060-96-2 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, [R-(R*,R*)]-, compd. with (-)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (2:3) (9CI) (CA INDEX NAME)

CM 1

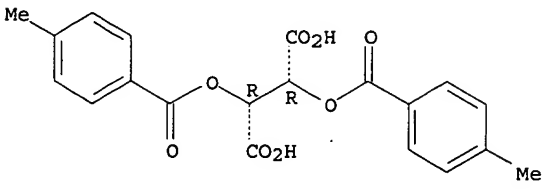
CRN 116655-76-6
CMF C19 H19 N O S



CM 2

CRN 32634-66-5
CMF C20 H18 O8

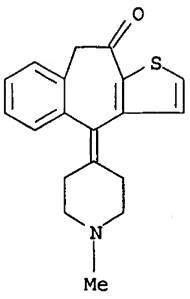
Absolute stereochemistry.



RN 127060-97-3 CAPLUS
CN Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with (-)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:2) (9CI) (CA INDEX NAME)

CM 1

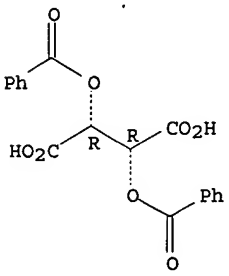
CRN 116655-76-6
CMF C19 H19 N O S



CM 2

CRN 2743-38-6
CMF C18 H14 O8

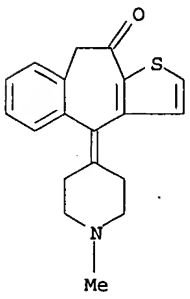
Absolute stereochemistry.



RN 127060-98-4 CAPLUS
CN Bicyclo[2.2.1]heptane-1-methanesulfonic acid, 7,7-dimethyl-2-oxo-, (1S)-, compd. with (+)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

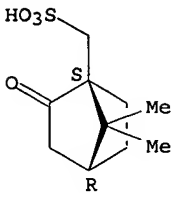
CRN 116655-75-5
CMF C19 H19 N O S



CM 2

CRN 3144-16-9
CMF C10 H16 O4 S

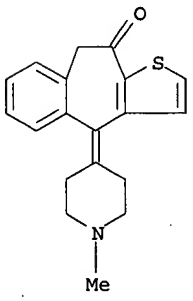
Absolute stereochemistry. Rotation (+).



RN 127060-99-5 CAPLUS
CN Butanedioic acid, 2,3-bis(benzoyloxy)-, [R-(R*,R*)]-, compd. with (+)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:2) (9CI) (CA INDEX NAME)

CM 1

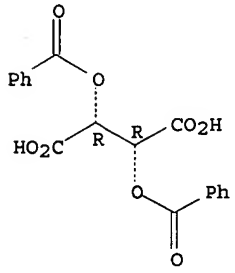
CRN 116655-75-5
CMF C19 H19 N O S



CM 2

CRN 2743-38-6
CMF C18 H14 O8

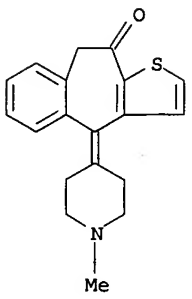
Absolute stereochemistry.



RN 127061-01-2 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, [S-(R*,R*)]-, compd. with (-)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (1:1) (9CI) (CA INDEX NAME)

CM 1

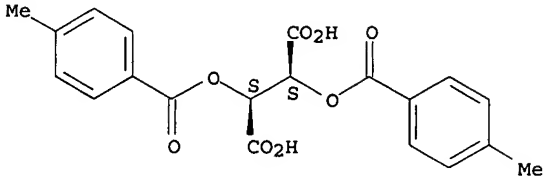
CRN 116655-76-6
CMF C19 H19 N O S



CM 2

CRN 32634-68-7
CMF C20 H18 O8

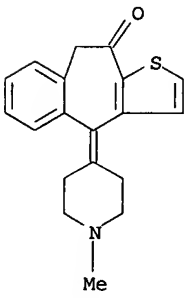
Absolute stereochemistry. Rotation (+).



RN 127061-02-3 CAPLUS
CN Butanedioic acid, 2,3-bis[(4-methylbenzoyl)oxy]-, [R-(R*,R*)]-, compd. with (+)-4,9-dihydro-4-(1-methyl-4-piperidinylidene)-10H-benzo[4,5]cyclohepta[1,2-b]thiophen-10-one (2:3) (9CI) (CA INDEX NAME)

CM 1

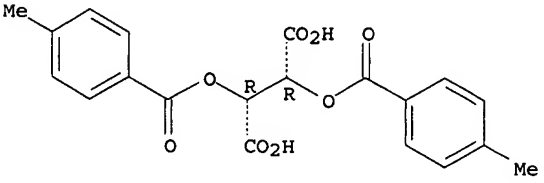
CRN 116655-75-5
CMF C19 H19 N O S



CM 2

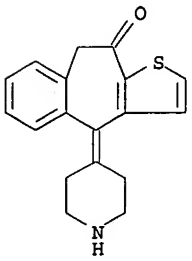
CRN 32634-66-5
CMF C20 H18 O8

Absolute stereochemistry.

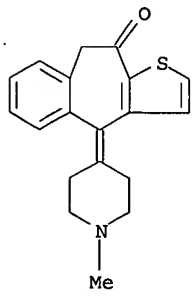


IT **116655-74-4P**

RL: SPN (Synthetic preparation); PREP (Preparation)
(prepn., resoln., and biol. activity of)
RN 116655-74-4 CAPLUS
IT **34580-20-6**
RL: RCT (Reactant); RACT (Reactant or reagent)
(reaction of, with Me iodide)
RN 34580-20-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(4-piperidinylidene)- (9CI) (CA INDEX NAME)



L8 ANSWER 16 OF 16 CAPLUS COPYRIGHT 2003 ACS
AN 1988:535061 CAPLUS
DN 109:135061
TI Use of cyclodextrins in isotachophoresis. V. The separation of ketotifen and its polar intermediate **enantiomers**
AU Jelinek, Ivan; Snopek, Jiri; Smolkova-Keulemansova, Eva
CS Res. Inst. Pharm. Biochem., Prague, 160 60, Czech.
SO Journal of Chromatography (1988), 439(2), 386-92
CODEN: JOCRAM; ISSN: 0021-9673
DT Journal
LA English
AB Isotachophoresis (ITP) using enantiospecific additives, i.e. .beta.-cyclodextrin and dimethyl-.beta.-cyclodextrin, was an effective method for the resoln. of the **enantiomers** of ketotifen and those of its intermediate. The optimization procedure, based on the monitoring of the max racemate load, (nr)max, confirms the importance of the cyclodextrin concn. Also, the ITP resoln. was strongly influenced by the choice of cyclodextrin.
IT **116655-74-4**
RL: PROC (Process)
(resoln. of, by isotachophoresis, cyclodextrins in)
RN 116655-74-4 CAPLUS
IT **116655-75-5 116655-76-6**
RL: PROC (Process)
(sepn. of, by isotachophoresis, cyclodextrins in)
RN 116655-75-5 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (R)- (9CI) (CA INDEX NAME)



RN 116655-76-6 CAPLUS
CN 10H-Benzo[4,5]cyclohepta[1,2-b]thiophen-10-one, 4,9-dihydro-4-(1-methyl-4-piperidinylidene)-, (S)- (9CI) (CA INDEX NAME)

10069663